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## (54) Antimicrobial pharmaceutical composition.

(57) The invention relates to a synergistic, anti-microbial pharmaceutical composition containing 0.01 to 50 % by weight of a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I).

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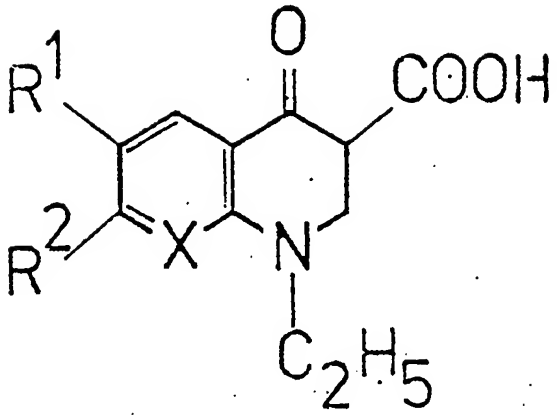
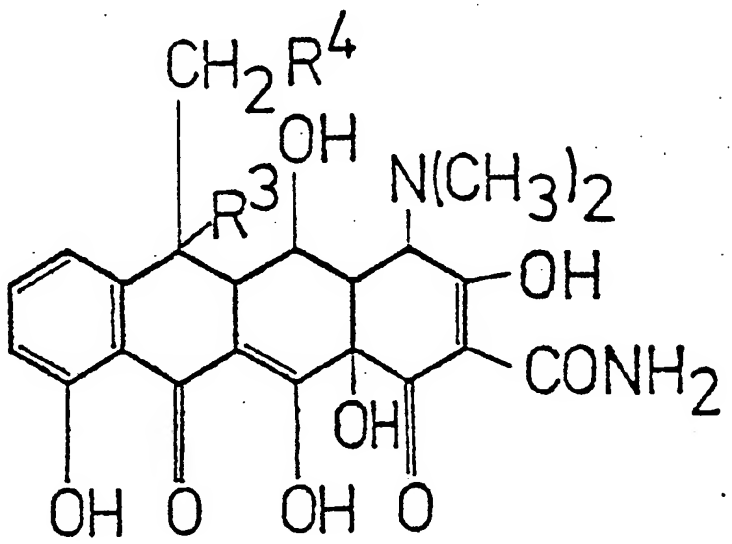


(I)

wherein
X is carbon or nitrogen;
$R^1$ is hydrogen or fluorine;
$R^2$ is methyl, piperazino or methylpiperazino group; or
$R^1$ and $R^2$ together are a methylenedioxy group; and 0.01 to 95 % by weight of a tetracycline derivative of the general formula (II),

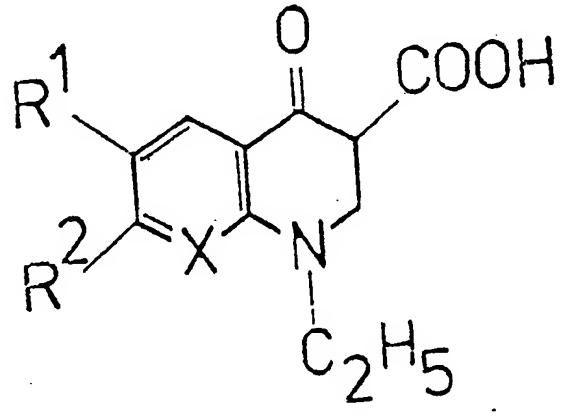


(II)

wherein
$R^3$ and $R^4$ are hydrogen; or
$R^3$ and $R^4$ together represent an additional chemical bond,
in an 1:1 to 1:20 ratio of the compound of the general formula (I) to the compound of the general formula (II), optionally in an admixture with an amount required to 100 % by weight of an inert, solid or liquid carrier such as magnesium carbonate, magnesium stearate, starch, talc, cyclodextrine or water and other additives such as filling, disintegrating, sliding and emulsifying agents.

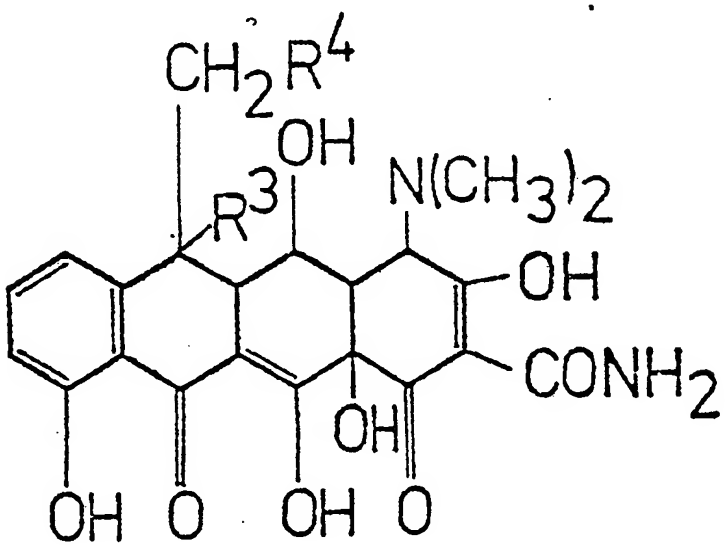
# PHARMACEUTICAL COMPOSITION

This invention relates to synergistic, anti-microbial pharmaceutical compositions containing a quinolinecarboxylic acid derivative or a naphthyridine-carboxylic acid derivative of the general formula (I),



(I)

wherein
X is carbon or nitrogen;
$R^2$ is hydrogen or fluorine;
$R^2$ is methyl, piperazino or methylpiperazino group; or
$R^1$ and $R^2$ together are a methylenedioxy group;
and a tetracycline derivative of the general formula (II),



(II)

wherein
$R^3$ and $R^4$ are hydrogen; or
$R^3$ and $R^4$ together represent an additional chemical bond,
as active ingredients.

In an other aspect of the invention, there is provided a process for the preparation of these compositions.

In the antimicrobial therapy, a continuous combat exists between the adaptation capability of microorganisms (development of resistance) and the preparation of novel drugs.

In the case of novel drugs, the adaptation capability, i.e. the resistance usually develops within a shorter or longer period. It can be expected that the development of the resistance becomes particularly rapid when the new substance is a derivative of a drug previously used for a long time since in this case, the resistance developed to the starting compound will of course more rapidly be modified for the derivatives.

The development of the resistance can be delayed by the simultaneous administration, i.e. combination of several active compounds whereby the methabolism of the microorganisms is attacked at several points at the same time. This results that the resistance of the microorganisms to the combination hardly or long afterwards develops thus, the desired "microbicidal" (killing) effect is strengthened.

In the antimicrobial therapy, nalidixic acid has been used for a long time as active ingredient. It was published that from its derivatives, norfloxacin (Belgian patent specification. No. 863,429) and perfloxacin (Belgian patent specifications Nos. 870,576 and 870,917) show a highly favourable effect on gram-negative pathogens whereas their effect on gram-positive pathogens is more moderate.

Tetracycline is also a long-known antimicrobial substance. Out of its derivatives, doxicycline has a very favourable effect on gram-positive pathogens and a moderate effect on gram-negative ones.

The aim of the invention is to prepare broad-spectrum pharmaceutical compositions by combining these two types of active substances and thereby to inhibit the development of resistance.

When combining tetracycline derivatives with the quinoline-carboxylic acid derivatives or naphthyridine-carboxylic acid derivatives of the general formula (I), it was surprisingly observed that, in addition to the realization of the aim of the invention, a high-level synergistic action of these two types of active substances occurred, whereby the effective doses could strongly be decreased with the important advantages of less side-effects and a cheaper therapy.

Thus, the present invention relates to the preparation of a synergistic, antimicrobial pharmaceutical composition containing a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I), wherein

X is carbon or nitrogen;

$R^1$ is hydrogen or fluorine;

$R^2$ is methyl, piperazino or methylpiperazino group; or

$R^1$ and $R^2$ together are a methylenedioxy group; and a tetracycline derivative of the general formula (II), wherein

$R^3$ and $R^4$ are hydrogen; or

$R^3$ and $R^4$ together represent an additional chemical bond,

as active ingredients, which comprises mixing together 0.01 to 50 % by weight of a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I), wherein X, $R^1$ and $R^2$ are the same as defined above and 0.01 to 95 % by weight of a tetracycline derivative of the general formula (II), wherein $R^3$ and $R^4$ are the same as defined above while maintaining the ratio of the compound of the general formula (I) to the compound of the general formula (II) as 1:1 to 1:20, and optionally inert, solid or liquid carriers, preferably magnesium carbonate, magnesium stearate, starch, talc, cyclodextrin or water as well as binding, disintegrating, emulsifying, sliding agents and lubricants as additives and formulating them in a known way to a pharmaceutical composition suitable for therapeutical application.

In the process of the invention, preferably a compound of the general formula (I), wherein X, $R^1$ and $R^2$ are as defined above, suitably norfloxacin (1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-piperazinoquinoline-3-carboxylic acid) and doxicycline (4-dimethylamino-1,11-dioxo-6-methyl-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamid) may be used as active ingredients of the combination.

Similarly, oxolinic acid (1,4-dihydro-1-ethyl-6,7-methylenedioxy-4-oxoquinoline-3-carboxylic acid) and methacycline (4-dimethylamino-1,11-dioxo-6-methylene-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamide) may preferably be used in the combination according to the invention.

According to a preferred embodiment of the invention, the active ingredients are used in an 1:1 ration. If desired, the compositions may contain also other active ingredients, (such as antibiotics, chemotherapeutics or the like).

The pharmaceutical compositions according to the invention may be formulated in solid forms, such as granulates, tablets, capsules, dragées and suppositories, semisolid forms, such as ointments and the like or liquid forms, such as injectable solutions, emulsions or suspensions. Preferably gels, ointments, dusting powders for wounds, injectable solutions and suspensions as well as the combinations of powder and solvent ampoules are prepared.

Depending on the formulation, magnesium carbonate, magnesium stearate, starch, talc and water as commonly used carriers, cyclodextrin as a novel carrier as well as other additives such as vehicles,

disintegrating, sliding and emulsifying agents may be used.

The compositions according to the invention may be administered in oral, parenteral or rectal route or may be topically used.

The orally useful compositions are e.g. granulates, tablets, capsules or dragées. Parenterally useful compositions are e.g. the aqueous emulsions, suspensions or solutions. Ointments, aqueous or oily emulsions and suspensions as well as sprays may topically be applied.

The pharmaceutical compositions containing the synergistic active ingredient combination may be used in the veterinary medicine, too, e.g. in the form of a powder mixed to the fodder, or in the form of a solution added to the drinking fluid of the animals. For this purpose, compositions containing a combination of oxolinic acid and methacycline are preferably used.

The in vitro biological activity of the compositions according to the invention are shown in Tables I to V.

The international resistant and/or polyresistant human-pathogenic and/or veterinary-pathogenic microorganisms used in these investigations were as follows.

1.) Vibrio parahaemolyticus CCM.5938.
2.) Pseudomonas fluorescens CCM.2115.
3.) Pseudomonas pictorum CCM.284.
4.) Pseudomonas acidovorans CCM.283.
5.) Proteus vulgaris CCM.1799.
6.) Proteus mirabilis CCM.1944.
7.) Shigella sonnei CCM.1373.
8.) Salmonella typhimurium CCM.5445
9.) Salmonella cholerae suis CCM.5438.
10.) Escherichia coli DSM.30038.
11.) Escherichia coli CCM.5863.
12.) Escherichia coli CCM.5172.
13.) Klebsiella pneumoniae CCM.1848.
14.) Serratia marcescens CCM.303.
15.) Pasteurella multocida CCM.5419.
16.) Staphylococcus aureus CCM.885.
17.) Staphylococcus aureus CCM.2317.
18.) Staphylococcus aureus CCM.2326.
19.) Streptococcus agalactiae CCM.5534.
20.) Streptococcus disgalactiae CCM.5548.
21.) Bacillus subtilis ATCC.6633.
22.) Micrococcus flavus ATCC.10240.
23.) Bacillus licheniformis CCM.2182.
24.) Bacillus licheniformis CCM.2205.
25.) Pseudomonas putrefaciens Sz-III-156.
26.) Pseudomonas fluorescens putida M-III-21.
27.) Pseudomonas fluorescens putida K-I-86.

Abbreviations used hereinabove and hereinafter are as follows:

ATCC = The American Type Culture Collection
CCM = Czechoslovak Collection of Microorganisms
DSM = Deutsche Sammlung für Mikroorganismen
µg/ml = microgram/millilitre

The investigations were carried out on a Difco Bouillon medium (in the case of bacteria) or on a modified Difco Bouillon medium (in the case of vibrios).

The inoculation was made with a germ number of $5 \times 10^5$/ml. The incubation lasted 24 hours at 37 °C.

It is obvious from the data of the Tables that, due to the synergistic effect, from the combination a part and in some cases even a fraction of the amounts of the active ingredients, (as calculated for their individual activity), is sufficient to achieve an identical effect.

Table I

| Combination of Nalidixic Acid with Doxicycline | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MIC value µg/ml | | | | Decrease of the MIC value by the combination % | | | Effect, % | |
| | | | | Combination | | | | | | |
| | | Nal | Dox | Nal | Dox | Nal | Dox | Nal + Dox | Additive | Synerg. |
| Vibrio p. haemolyticus | CCM.5938. | 5 | 0.5 | 0.5 | 0.25 | 10 | 50 | 30 | 60 | 40 |
| Pseudomonas pictorum | CCM.284. | 25 | 0.75 | 2.5 | 0.075 | 10 | 10 | 10 | 20 | 80 |
| Proteus vulgaris | CCM.1799. | 50 | 10 | 5 | 2.5 | 10 | 25 | 16.5 | 35 | 65 |
| Proteus mirabilis | CCM.1944. | 10 | 25 | 2.5 | 5 | 25 | 20 | 22.5 | 45 | 55 |
| Salmonella typhimurium | CCM.5445. | 50 | 10 | 5 | 5 | 10 | 50 | 30 | 60 | 40 |
| Salmonella cholerae suis | CCM.5438. | 25 | 0.5 | 2.5 | 0.05 | 10 | 10 | 10 | 20 | 80 |
| Escherichia coli | DSM.30038. | 50 | 5 | 5 | 0.5 | 10 | 10 | 10 | 20 | 80 |
| Escherichia coli | CCM.5863. | 25 | 5 | 2.5 | 0.5 | 10 | 10 | 10 | 20 | 80 |
| Escherichia coli | CCM.5172. | 50 | 2.5 | 5 | 0.5 | 10 | 20 | 15 | 30 | 70 |
| Pasteurella multocida | CCM.5419. | 50 | 0.25 | 5 | 0.025 | 10 | 10 | 10 | 20 | 80 |
| Staphylococcus aureus | CCM.2317. | 100 | 0.25 | 10 | 0.05 | 10 | 20 | 25 | 30 | 70 |
| Staphylococcus aureus | CCM.2326. | 100 | 0.25 | 10 | 0.075 | 10 | 30 | 20 | 40 | 60 |
| Streptococcus disgalactiae | CCM.5548. | 75 | 0.5 | 10 | 0.25 | 13.3 | 50 | 31.6 | 63.3 | 36.7 |
| Abbreviations: Nal = nalidixic acid<br>Dox = doxicycline | | | | | | | | | | |

Table II

| Combination of Oxolinic acid with Doxicycline | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MIC value µg/ml | | | | Decrease of the MIC value by the combination % | | | Effect, % | |
| | | | | Combination | | | | | | |
| | | Ox | Dox | Ox | Dox | Ox | Dox | Ox + Dox | Additive | Synerg. |
| Vibrio p-Haemolyticus | CCM.5939. | 1 | 0.5 | 0,1 | 0.25 | 10 | 50 | 30 | 60 | 40 |
| Pseudomonas fluorescens | CCM.2115. | 10 | 0.5 | 0.25 | 0.25 | 2.5 | 50 | 26.3 | 52.5 | 47.5 |
| Pseudomonas acidovorans | CCM.283. | 0.5 | 0.25 | 0.05 | 0.05 | 10 | 20 | 15 | 30 | 70 |
| Pseudomonas pictorum | CCM.284. | 5 | 0.75 | 0.5 | 0.075 | 10 | 10 | 10 | 20 | 80 |
| Shigella sonnei | CCM.1373. | 0.75 | 1 | 0.075 | 0.05 | 10 | 5 | 7.5 | 15 | 85 |
| Escherchia coli | CCM.5863. | 5 | 5 | 0.75 | 0.75 | 15 | 15 | 15 | 30 | 70 |
| Escherichia coli | CCM.5172. | 2.5 | 2.5 | 0.75 | 0.75 | 30 | 30 | 30 | 60 | 40 |
| Staphylococcus aureus | CCM.885. | 25 | 1 | 2.5 | 0.1 | 10 | 10 | 10 | 20 | 80 |
| Staphylococcus Aureus | CCM.2317. | 10 | 0.25 | 1 | 0.025 | 10 | 10 | 10 | 20 | 80 |
| Bacillus subtilis | ATCC.6633. | 0.75 | 0.05 | 0.1 | 0.025 | 13.3 | 50 | 31.6 | 63.3 | 36.7 |
| Bacillus cereus | CCM.2010. | 5 | 0.5 | 0.5 | 0.25 | 10 | 50 | 30 | 60 | 40 |
| Abbreviations: Ox = oxolinic acid<br>Dox = doxicycline | | | | | | | | | | |

Table III

| Combination of Norfloxacin with Doxicycline | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MIC value µg/ml | | | | Decrease of the MIC value by the combination % | | | Effect, % | |
| | | | | Combination | | | | | | |
| | | Norf | Dox | Norf | Dox | Norf | Dox | Norf + Dox | Additive | Synerg. |
| Vibrio p. haemolyticus | CCM.5938 | 0.5 | 0.5 | 0.25 | 0.1 | 50 | 20 | 35 | 70 | 30 |
| Pseudomonas fluorescens | CCM.2115. | 0.25 | 0.5 | 0.05 | 0.05 | 20 | 10 | 15 | 30 | 70 |
| Pseudomonas pictor. | CCM.284. | 0.75 | 0.75 | 0.1 | 0.25 | 13.3 | 33.3 | 23.3 | 46.6 | 53.4 |
| Proteus vulg. | CCM.1799. | 0.1 | 10 | 0.01 | 5 | 10 | 50 | 30 | 60 | 40 |
| Shigella sonnei | CCM.1373. | 0.1 | 1 | 0.01 | 0.5 | 10 | 50 | 30 | 60 | 40 |
| Salmon. typhimus. | CCM.5445. | 0.5 | 10 | 0.075 | 2.5 | 15 | 25 | 20 | 40 | 60 |
| Salmon. Choleraesuis | CCM.5438. | 0.5 | 0.5 | 0.05 | 0.05 | 10 | 10 | 10 | 20 | 80 |
| Esch. Coli | DSM.30038. | 0.1 | 5 | 0.025 | 0.75 | 25 | 15 | 20 | 40 | 60 |
| Esch. coli | CCM.5863. | 0.25 | 5 | 0.05 | 0.75 | 20 | 15 | 17.5 | 35 | 65 |
| Past. multocida | CCM.5419. | 0.5 | 0.25 | 0.05 | 0.025 | 10 | 10 | 10 | 20 | 80 |
| Staph. aureus | CCM.885. | 5 | 1 | 1 | 0.25 | 20 | 25 | 22.5 | 45 | 55 |
| Strept. disgalact. | CCM.5548. | 2.5 | 0.5 | 0.75 | 0.1 | 30 | 20 | 25 | 50 | 50 |
| Abbreviations: Norf = Norfloxacin<br>Dox = doxicycline | | | | | | | | | | |

Table IV

| Combination of Pefloxacin with Doxicycline | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | MIC value µg/ml | | | | Decrease of the MIC value by the combination % | | | Effect, % | |
| | | | | Combination | | | | | | |
| | | Pefl | Dox | Pefl | Dox | Pefl | Dox | Pefl + Dox | Additive | Synerg. |
| Vibrio p. haemolyticus | CCM.5938. | 0.5 | 0.5 | 0.75 | 0.25 | 15 | 50 | 32.5 | 65 | 35 |
| Proteus vulgaris | CCM.1799. | 0.5 | 10 | 0.1 | 0.05 | 20 | 0.5 | 10.2 | 20.5 | 79.5 |
| Proteus mirabilib | CCM.1944. | 0.5 | 25 | 0.075 | 2.5 | 15 | 10 | 12.5 | 25 | 75 |
| Shigella sonnei | CCM.1373. | 0.25 | 1 | 0.05 | 0.1 | 20 | 10 | 15 | 30 | 70 |
| Salmon. typhimur | CCM.5445. | 2.5 | 10 | 0.5 | 2.5 | 20 | 25 | 22.5 | 45 | 55 |
| Salmon. choleraesuis | CCM.5438. | 1 | 0.5 | 0.1 | 0.05 | 10 | 10 | 10 | 20 | 80 |
| Esch. coli | DSM.30038. | 1 | 5 | 0.1 | 0.5 | 10 | 10 | 10 | 20 | 80 |
| Esch. coli | CCM.5863. | 1 | 5 | 0.1 | 1 | 10 | 20 | 15 | 30 | 70 |
| Klebs. pneumon. | CCM.1848. | 0.75 | 2.5 | 0.075 | 1 | 10 | 40 | 25 | 50 | 50 |
| Serratia marcesc. | CCM.303. | 0.5 | 25 | 0.1 | 10 | 20 | 40 | 30 | 60 | 40 |
| Past. multocida | CCM.5419. | 0.25 | 0.25 | 0.05 | 0.05 | 20 | 20 | 20 | 40 | 60 |
| Strept. disgalact. | CCM.5548. | 10 | 0.5 | 1 | 0.25 | 10 | 50 | 30 | 60 | 40 |
| Pseud. putrefac. | Sz-III-156. | 0.25 | 0.5 | 0.05 | 0.075 | 20 | 15 | 17.5 | 35 | 65 |
| Pseud. fluoresc. putida | M-III-21. | 2.5 | 2.5 | 0.5 | 0.75 | 20 | 30 | 25 | 50 | 50 |
| Pseud. flouresc. putida | K-I-86. | 2.5 | 0.25 | 0.05 | 0.05 | 2 | 20 | 11 | 22 | 78 |

Abbreviations: Pefl = pefloxacin
Dox = doxicycline

Table V

Combination of Oxolinic acid with Methacycline

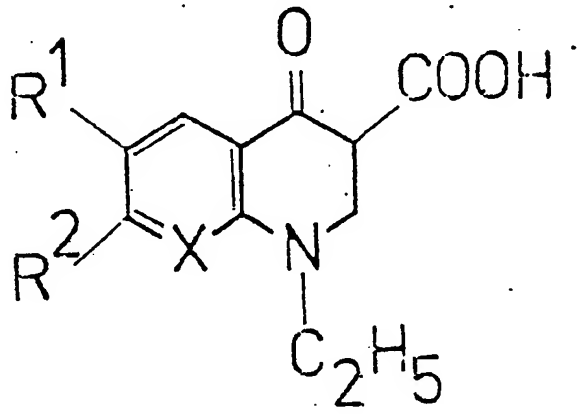
| | | MIC value /ug/ml | | | | Decrease of the MIC value by the combination % | | | Effect, % | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Combination | | | | | | |
| | | Ox | Methac | Ox | Methac | Ox | Methac | Ox + Methac | Additive | Synerg. |
| Vibrio p. haemolyticus | CCM.5938. | 1 | 1 | 0.25 | 0.1 | 25 | 10 | 17.5 | 35 | 65 |
| Pseud. fluoresc. | CCM.2115. | 2.5 | 0.5 | 0.75 | 0.1 | 30 | 20 | 25 | 50 | 50 |
| Esch. coli | DSM.30038. | 1 | 2.5 | 0.25 | 0.25 | 25 | 10 | 17.5 | 35 | 65 |
| Esch. coli | CCM.5863. | 5 | 2.5 | 0.25 | 0.25 | 5 | 10 | 7.5 | 15 | 85 |
| Esch. coli | CCM.5172. | 2.5 | 2.5 | 0.25 | 0.25 | 10 | 10 | 10 | 20 | 80 |

Abbreviations: Ox = oxolinic acid

Methac = methacycline

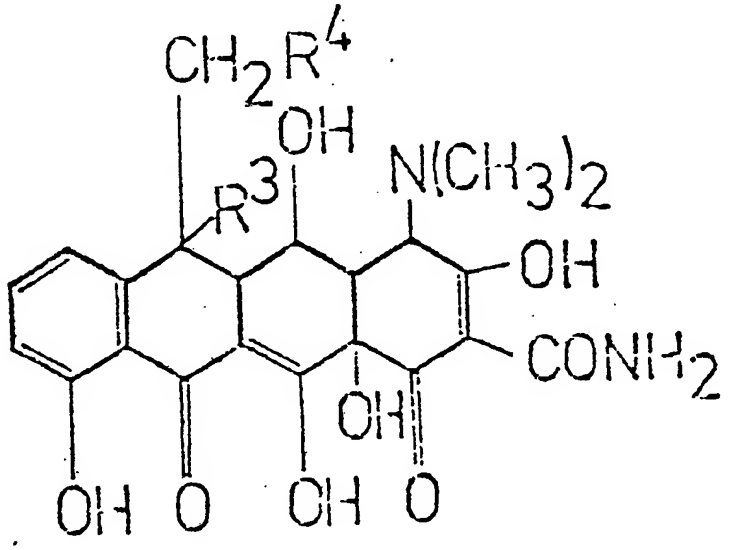
## Claims

1. Synergistic, antimicrobial pharmaceutical compostion which comprises 0.01 to 50 % by weight of a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I),



(I)

wherein
X is carbon or nitrogen;
$R^1$ is hydrogen or fluorine;
$R^2$ is methyl, piperazino or methylpiperazino group; or
$R^1$ and $R^2$ together are a methylenedioxy group; and 0.01 to 95 % by weight of a tertracycline derivative of the general formula (II),



(II)

wherein
$R^3$ and $R^4$ are hydrogen; or
$R^3$ and $R^4$ together represent an additional chemical bond,
in an 1:1 to 1:20 ratio of the compound of the general formula (I) to the compound of the general formula (II), optionally in an admixture with an amount required to 100 % by weight of an inert, solid or liquid carrier such as magnesium carbonate, magnesium stearate, starch, talc, cyclodextrine or water and other additives

such as filling, disintegrating, sliding and emulsifying agents.

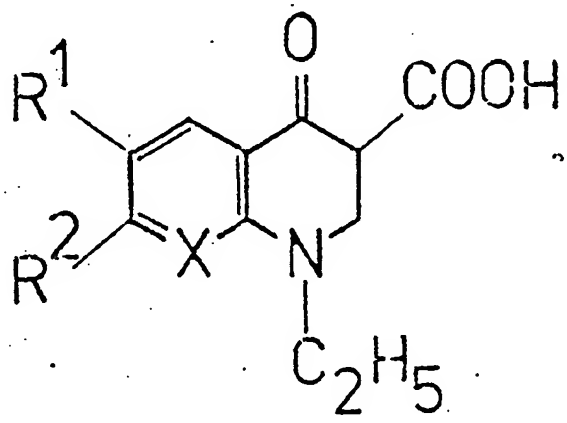
2. A composition as claimed in claim 1 which comprises a quinolinecarboxylic acid derivative or naphthyridinecarboxylic acid derivative of the general formula (I), wherein X, $R^1$ and $R^2$ are as defined in claim 1 and doxicycline (4-dimethylamino-1,11-dioxo-6-methyl-1,4,4a,5,5a,6,11,12,12a-octahydro-3,5,10,12,-12a-pentahydroxy-2-naphthacenecarboxamide as active ingredients.

3. A composition as claimed in claim 2, which comprises norfloxacin (1,4-dihydro-1-ethyl-6-fluoro-4-oxo-7-piperazinoquinoline-3-carboxylic acid) and doxicycline as active ingredients.

4. A composition as claimed in claim 1, which comprises oxolinic acid (1,4-dihydro-1-ethyl-6,7-methylene-dioxy-4-oxoquinoline-3-carboxylic acid) and methacycline (4-dimethylamino-1,11-dioxo-6-methylene-1,4,4a,5,5a,6,-11,12,12a-octahydro-3,5,10,12,12a-pentahydroxy-2-naphthacenecarboxamide) as active ingredients.

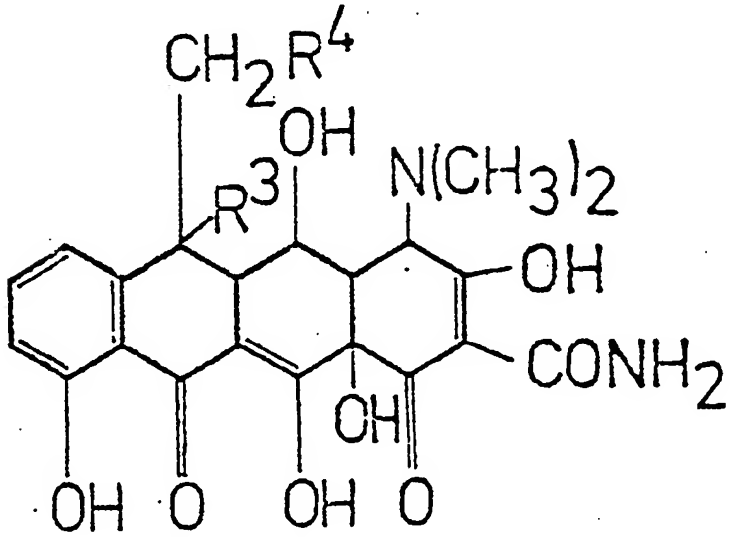
5. A composition as claimed in claim 1, which comprises the active ingredients in an 1:1 ratio.

6. Process for the preparation of a synergistic, antimicrobial, pharmaceutical composition containing a quinolinecarboxylic acid derivative or a naphthyridine-carboxylic acid derivative of the general formula (I),



(I)

wherein
X is carbon or nitrogen;
$R^1$ is hydrogen or fluorine;
$R^2$ is methyl, piperazino or methylpiperazino group; or
$R^1$ and $R^2$ together are a methylenedioxy group; and a tetracycline derivative of the general formula (II),



(II)

wherein
$R^3$ and $R^4$ are hydrogen; or
$R^3$ and $R^4$ together represent an additional chemical bond,
as active ingredients, which comprises mixing together 0.01 to 50 % by weight of a quinolinecarboxylic acid derivative or a naphthyridinecarboxylic acid derivative of the general formula (I), wherein X, $R^1$ and $R^2$ are the same as defined above and 0.01 to 95 % by weight of a tetracycline derivative of the general formula (II), wherein $R^3$ and $R^4$ are the same as defined above while maintaining the ratio of the compound of the general formula (I) to the compound of the general formula (II) as 1:1 to 1:20, and optionally inert, solid or liquid carriers, preferably magnesium carbonate, magnesium stearate, starch, talc, cyclodextrin or water as well as binding, disintegrating, emulsifying, sliding agents and lubricants as additives and formulating them in a known way to a pharmaceutical composition suitable for therapeutical application.

European Patent Office

# EUROPEAN SEARCH REPORT

Application Number

EP 88 30 6598

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
|---|---|---|---|
| X | GB-A-2 035 800 (AUSONIA FARMACEUTICI SRL)<br>* Page 1, line 5 - page 2, line 31 * | 1-6 | A 61 K 31/65 //<br>(A 61 K 31/65<br>A 61 K 31:435)<br>(A 61 K 31/65<br>A 61 K 31:495)<br>(A 61 K 31/65<br>A 61 K 31:47 ) |
| X | FR-A-2 563 433 (ALLATORVOSTUDOMANYI EGYETEM)<br>* Page 10, lines 1-29; claims 1-5 * | 1-6 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 28-10-1988 | BRINKMANN C. |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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